Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted?


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Seventy-five children treated for craniopharyngioma between 1973 and 1994 were studied to demonstrate which pre- and intraoperative factors were indicative of a poor outcome as defined by a quantitative assessment of morbidity. This involved a retrospective review of 65 patients and a prospective study of 10 patients focused on clinical details and cranial imaging and a follow-up “study assessment” of 66 survivors performed over the last 2 years. As part of the assessment, 65 patients underwent magnetic resonance imaging with a three-dimensional volume acquisition sequence 1.5 to 19.2 years after initial surgery. Predictors of high morbidity included severe hydrocephalus, intraoperative adverse events, and young age (≤ 5 years) at presentation. Predictors of increased hypothalamic morbidity included symptoms of hypothalamic disturbance already established at diagnosis, greater height (≥ 3.5 cm) of the tumor in the midline, and attempts to remove adherent tumor from the region of the hypothalamus at operation. Large tumor size, young age, and severe hydrocephalus were predictors of tumor recurrence, whereas complete tumor resection (as determined by postoperative neuroimaging) and radiotherapy given electively after subtotal excision were less likely to be associated with recurrent disease. Based on these findings, the authors propose an individualized, more flexible treatment approach whereby surgical strategies may be modified to provide long-term tumor control with the lowest morbidity.

Key Words • craniopharyngioma • hypothalamus • risk factors • morbidity score • outcome • magnetic resonance imaging

Controversy continues over the optimal management of childhood craniopharyngioma. Many neurosurgeons advocate complete tumor excision as the primary goal of treatment in every case, regardless of the age of the patient or the tumor’s size, consistency, or location, whereas most oncologists and radiotherapists remain vehement supporters of cranial irradiation, either as the sole treatment modality or as an adjuvant to limited surgical resection.

Advocates for radical tumor removal report that total surgical resection is possible in 70% to 90% of children, with an operative mortality rate of 0% to 11%. Approximately 25% to 30% of these children will experience tumor recurrence within 5 years from surgery, compared to estimates ranging up to 100% of patients following partial tumor removal without adjuvant therapy.

Although surgical mortality has been reduced with the advent of microsurgical techniques and improved endocrinological management in the perioperative period, there is a continued appreciation of the morbidity associated with attempted radical excision, particularly with regard to hypothalamic function. Thus, before deciding on a management plan, the neurosurgeon must consider the risks of hypothalamic or major vessel damage caused by aggressive surgery; cognitive deficit in the young brain or second tumors induced by irradiation; and increased morbidity as a result of recurrent disease.

We have studied 75 children with craniopharyngioma with the aim of demonstrating which pre- and intraoperative factors are associated with poor outcome, as determined by a quantitative assessment of morbidity. This has entailed a detailed follow-up “study assessment” in 66 survivors, 63 of whom underwent magnetic resonance (MR) imaging 1.5 to 19.2 years after initial surgery. We believe that evaluation of clinical and neuroradiological risk factors at diagnosis allows prediction of outcome and thus surgical strategies can be modified accordingly, and an individualized approach to treatment can be used.

Clinical Material and Methods

Patient Population

This study was approved by the local Standing Committee on Ethical Practice, and written parental or patient consent was obtained in all cases. Thirty-three girls and 42 boys between the ages of 1 and
Characteristics of patients with childhood craniopharyngioma as determined at presentation by preoperative neuroimaging investigations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tumor volume (51 patients)</td>
<td></td>
</tr>
<tr>
<td>&gt;100 ml</td>
<td>15 (29)</td>
</tr>
<tr>
<td>50–100 ml</td>
<td>7 (14)</td>
</tr>
<tr>
<td>&lt;50 ml</td>
<td>29 (57)</td>
</tr>
<tr>
<td>tumor height in midline (51 patients)</td>
<td></td>
</tr>
<tr>
<td>≥3.5 cm</td>
<td>26 (51)</td>
</tr>
<tr>
<td>&lt;3.5 cm</td>
<td>25 (49)</td>
</tr>
<tr>
<td>tumor components (73 patients)</td>
<td></td>
</tr>
<tr>
<td>&gt;50% cystic</td>
<td>47 (64)</td>
</tr>
<tr>
<td>&gt;50% solid</td>
<td>20 (27)</td>
</tr>
<tr>
<td>50:50 cystic/solid</td>
<td>6 (8)</td>
</tr>
<tr>
<td>grade of hydrocephalus (74 patients)*</td>
<td></td>
</tr>
<tr>
<td>0 (none; EI ≤30%)</td>
<td>34 (46)</td>
</tr>
<tr>
<td>1 (mild; EI 31%–39%)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>2 (moderate; EI 40%–49%)</td>
<td>15 (20)</td>
</tr>
<tr>
<td>3 (moderately severe; EI 50%–55%)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>4 (severe; EI &gt;55%)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

* EI = Evans’ index; for additional information see text.

TABLE 2
Morbidity in 75 patients with craniopharyngioma after initial surgery and at study assessment

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Morbidity Score Assigned</th>
<th>After Initial Surgery</th>
<th>At Study Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>endocrine†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>panhypopituitarism + impaired thirst</td>
<td>3</td>
<td>10 (13)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>panhypopituitarism</td>
<td>2</td>
<td>50 (67)</td>
<td>57 (76)</td>
</tr>
<tr>
<td>partial anterior pituitary deficiency ≤ DI</td>
<td>1</td>
<td>14 (19)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>no pituitary deficit</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>vision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA ≥6/60 both eyes</td>
<td>3</td>
<td>10 (13)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>VA 6/18 to &gt;6/60 or blind in one eye</td>
<td>2</td>
<td>29 (39)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>VA 6/9 to &gt;6/18 in one or both eyes</td>
<td>1</td>
<td>7 (9)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>normal vision</td>
<td>0</td>
<td>29 (39)</td>
<td>24 (32)</td>
</tr>
<tr>
<td>neurology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe motor disorder ± epilepsy</td>
<td>3</td>
<td>10 (13)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>mild-to-moderate motor disorder ± seizures</td>
<td>2</td>
<td>18 (24)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>signs only; no seizures</td>
<td>1</td>
<td>10 (13)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>normal neurology</td>
<td>0</td>
<td>37 (49)</td>
<td>25 (33)</td>
</tr>
<tr>
<td>education†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe learning difficulties ± severe behavioral problems</td>
<td>3</td>
<td>11 (15)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>moderate (IQ 71–79)</td>
<td>2</td>
<td>9 (12)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>mild (IQ 80–89)</td>
<td>1</td>
<td>25 (33)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>normal (IQ &gt;90)</td>
<td>0</td>
<td>30 (40)</td>
<td>28 (37)</td>
</tr>
<tr>
<td>hypotalamic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe hypotalamic syndrome</td>
<td>3</td>
<td>11 (15)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>moderate</td>
<td>2</td>
<td>16 (21)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>mild</td>
<td>1</td>
<td>14 (19)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>normal</td>
<td>0</td>
<td>34 (45)</td>
<td>33 (44)</td>
</tr>
<tr>
<td>death</td>
<td>15</td>
<td>0 (0)</td>
<td>9 (12)</td>
</tr>
</tbody>
</table>

† DI = diabetes insipidus; IQ = intelligence quotient; VA = visual acuity.
‡ Panhypopituitarism is complete anterior pituitary deficiency plus diabetes insipidus; in partial anterior pituitary deficiency, one or more anterior pituitary hormones are intact.
§ Severe learning disabilities include patients with IQ ≤ 70.

Clinical and Neuroimaging Investigations

Clinical Studies. Clinical data were obtained retrospectively from case notes in 65 cases; 10 cases diagnosed after October 1992 were studied prospectively. The clinical features under investigation included:

“Emergency Presentation”: This included children requiring an urgent surgical procedure for relief of hydrocephalus or optic pathway compression.

“Hypothalamic Disturbance at Presentation”: Children assigned to this category presented with a history of extreme weight loss or significant weight gain, or with behavioral, memory, or sleep–wake disturbances not attributable to hydrocephalus.

“Tumor Adherence”: Attention was given to whether the tumor was adherent to the hypothalamus or to major vessels at operation.

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“Postoperative Status”: The visual, endocrine, and neurodevelopmental status of the patient was determined as soon after surgery as possible and prior to any further treatment (surgery or irradiation).

Neuroimaging Studies. All available pre- and postoperative computerized tomography (CT) and/or MR images were reviewed by two members of the study team (B.E.K. and C.J.D.) and the following information was documented:

“Tumor dimensions,” including height, maximum transverse diameter, and maximum anteroposterior diameter, allowed calculation of tumor volume in 51 cases. 16.4 years (mean 6.6 years) who were diagnosed as having a craniopharyngioma and treated from 1973 to early 1994 were studied. At diagnosis 29 children were under 5 years, 33 between 5 and 10 years, and 13 over 10 years of age.

Neurosurgical Management

Primary surgical management entailed attempted complete tumor removal via a transcranial procedure in 58 patients and by the transsphenoidal approach in one patient. In 15 cases, the surgical aim was subtotal tumor excision and, in one case, aspiration of cyst contents alone. Prior to 1989, complete tumor removal was the goal of surgery in all but two cases; however, in 14 of 35 patients seen over the past 5 years, the aims of surgery have become more conservative. Seven neurosurgeons performed these procedures over the 21-year period studied with a range of five to 28 cases per surgeon.

Surgical approach was via right frontal craniotomy in 38 cases, right pterional craniotomy in 28 cases, bifrontal craniotomy in two cases, and right temporal craniotomy in one case. A left-sided approach (frontal, temporal, or pterional) was used in four patients. There were no perioperative deaths; however, nine children subsequently died from tumor or related sequelae 0.3 to 15.4 years (median 5.9 years) after their initial surgery.

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### TABLE 3

<table>
<thead>
<tr>
<th>Findings</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>at presentation (75 patients)</td>
<td></td>
</tr>
<tr>
<td>hypothalamic disturbance</td>
<td>17 (23)</td>
</tr>
<tr>
<td>hypothalamic involvement by tumor on preop neuroimaging</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>58 (77)</td>
</tr>
<tr>
<td>no</td>
<td>16 (21)</td>
</tr>
<tr>
<td>unknown</td>
<td>1 (1)</td>
</tr>
<tr>
<td>tumor components in hypothalamic region (58 patients)</td>
<td></td>
</tr>
<tr>
<td>cystic</td>
<td>32 (55)</td>
</tr>
<tr>
<td>solid</td>
<td>12 (21)</td>
</tr>
<tr>
<td>mixed</td>
<td>12 (21)</td>
</tr>
<tr>
<td>unknown</td>
<td>2 (3)</td>
</tr>
<tr>
<td>at initial surgery (75 patients)</td>
<td></td>
</tr>
<tr>
<td>tumor adherence to hypothalamus</td>
<td>17 (23)</td>
</tr>
<tr>
<td>tumor removal from hypothalamus (58 patients)</td>
<td></td>
</tr>
<tr>
<td>attempted removal</td>
<td>43 (74)</td>
</tr>
<tr>
<td>left alone</td>
<td>15 (26)</td>
</tr>
<tr>
<td>at study assessment (63 patients)</td>
<td></td>
</tr>
<tr>
<td>grade of hypothalamic damage on magnetic resonance imaging</td>
<td></td>
</tr>
<tr>
<td>0 (no visible damage)</td>
<td>18 (29)</td>
</tr>
<tr>
<td>1 (floor of third ventricle thickened ± tumor)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>2 (floor of third ventricle thinned/distorted)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>3 (small breach in tuber cinereum)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>4 (more extensive breach than Grade 3, or Grades 2 + 3)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>5 (floor of third ventricle completely deficient)</td>
<td>17 (27)</td>
</tr>
</tbody>
</table>

(Some of the early CT scans did not have a scale to permit quantification of tumor size.)

“Height of the tumor in the midline” from the superior aspect of the pituitary fossa to the highest point of the tumor was recorded as a possible indicator of the extent of hypothalamic involvement.

“Number of intracranial compartments involved by tumor” was used as a further index of tumor size. The seven compartments coded included intrasellar, suprasellar, unilateral frontal, bilateral frontal, unilateral temporal, bilateral temporal, and posterior fossa involvement.

“Tumor components”: The proportion of solid and cystic components was assessed for the entire tumor as well as for any tumor within the hypothalamic region.

“Hydrocephalus” was graded as mild (1), moderate (2), moderately severe (3), or severe (4) using the Evans’ Index (maximal width of the frontal horns/maximal width of the inner skull × 100%) for assessment of ventricular size (Table 1).

### Study Assessment and Morbidity Score

Over the past 2 years clinical and radiological follow-up assessments have been undertaken in the 66 survivors. Clinical assessments included evaluation of endocrine, ophthalmological, neurological, neuropsychological and psychiatric status, and radiological assessments included MR imaging in 63 patients 1.5 to 19.2 years (mean 6.4 years) after initial surgery. A “morbidity score” was calculated for each patient immediately after surgery and at the study assessment. This was based on five clinical parameters with a maximum score of 15 (Table 2). The nine children who died before the study assessment were given the maximum score.

**Endocrine Function.** All patients received a formal assessment of anterior pituitary function after their initial surgery, using standard tests of hypothalamopituitary function. The diagnosis of diabetes insipidus was made on the basis of urine output, measurements of plasma and urine osmolality, and clinical response to intranasal administration of desmopressin.

**Visual Function.** Children unable to cooperate in a formal assessment of visual acuity were given a score based on the results of visual evoked responses.

**Neurological Assessments.** Patients were divided into groups on the basis of observed abnormalities of motor function (Table 2). “Severe motor disorder” comprised either bilateral limb involvement or a dense hemiplegia that necessitated dependence on others for mobility outside the home; “mild-to-moderate motor disorder” comprised those patients having a hemiparesis, including those whose deficit was severe but allowed community walking; “signs only” represented those with neurological signs but minimal or no loss of function.

**Psychological Assessment.** Learning difficulties were assessed by standard tests of intelligence and memory. Nine children could not attempt or complete testing because they exhibited disturbed behavior or because their intellect was too impaired. In those cases, direct observation of behavior, reports from parents and teachers, and details of educational placement and requirements for remedial support at the time of follow-up evaluation were considered when scoring morbidity.

**Hypothalamic Function.** Hypothalamic disturbance was graded as “mild” if there was postoperative obesity (body mass index > +2 standard deviation) without other change in affect or behavior indicative of hypothalamic dysfunction; “moderate” if there was an obvious period of hyperphagia and an associated change in affective behavior or memory in addition to obesity or weight gain; and “severe” if hyperphagia and weight gain were extreme and other clinical manifestations, such as impaired thirst, rage behavior, or disturbances of thermoregulation, memory, and sleep–wake pattern coexisted.

**Magnetic Resonance Imaging and Scoring System**

Magnetic resonance imaging was performed in 63 patients using a 1.5-tesla system (Magnetom SP 4000; Siemens, Erlangen, Germany) and a scale was devised, which ranged from 0 (no visible damage) to 5 (floor of the third ventricle completely deficient) to quantify the extent of hypothalamic damage, as determined by sagittal T1 sequences and a T2-weighted three-dimensional volume acquisition reconstructed in the sagittal plane (Table 3). A score for hypothalamic morbidity was derived by combining the MR imaging score of hypothalamic damage and the hypothalamic component of the clinical score, the maximum score being 8.

### Results

#### Clinical Studies

**Emergency Presentation.** Nineteen children (25%) required an initial surgical procedure for relief of hydro-
cephalus (14 cases), decompression of the optic nerves and chiasma (three cases), or both (two cases). All five children needing urgent visual pathway decompression were virtually blind by the time of referral. Of the patients requiring relief of hydrocephalus, five presented with an acute deterioration in their level of consciousness.

Hypothalamic Disturbance. Seventeen patients (23%) had evidence of hypothalamic dysfunction at presentation. In 11 cases there was a history of weight gain extending up to 3.5 years (median 1 year) before diagnosis; in three cases there was extreme weight loss; and in three cases disturbances of behavior or memory were the predominant hypothalamic symptoms.

Intraoperative Complications and Tumor Adherence. One or more complications occurred in 22 cases (29%) at the time of surgery. Arterial bleeding, usually from the carotid bifurcations, was recorded in nine patients. Definite damage to the left middle cerebral artery occurred during dissection in one case, and significant spasm of the right internal carotid artery was recorded in two cases. Profuse venous hemorrhage occurred in six patients and seven patients sustained trauma to the undersurface of the right frontal lobe.

The tumor was densely adherent to the carotids or their major branches in six of the 10 patients who had intraoperative arterial bleeding or definite arterial damage. In the entire group, tumor was adherent to major vessels in 12 cases, to the hypothalamus in 14 cases, and to both in three cases.

The surgical complication rate did not decrease significantly over the 21-year period studied.

Neuroimaging Studies

Tumor characteristics at presentation are summarized in Table 1. Tumor volume varied from 1.4 to 471.0 ml (median 41.0 ml) and height from the top of the pituitary fossa in the midline to the highest point of the tumor ranged from 0.4 to 5.6 cm (median 3.5 cm). Tumor characteristics in relation to the hypothalamus are shown in Table 3.

Hydrocephalus. Forty (54%) of 74 patients had hydrocephalus at presentation (Table 1) and 24 had some form of ventricular drainage procedure performed either pre-, peri-, or postoperatively. Of the 16 children with Grade 3 (moderately severe) or 4 (severe) hydrocephalus, 11 required ventricular drainage prior to tumor surgery.

Intracranial Compartments. Of 73 sets of images in which the number of intracranial compartments involved by tumor could be determined, one or two compartments were occupied in 32 cases, three or four compartments in 22 cases, and five or more compartments in 19 cases.

Patient Outcome

Extent of Surgical Resection. Total tumor excision was the aim of surgery in 59 patients. This was thought to have been achieved in 39 cases, as assessed by the surgeon at operation; however, on postoperative neuroimaging there was evidence of residual tumor (including images with small flecks of residual calcification) in 44 of the 73 patients whose films were available for analysis (Fig. 1).

There was a significant difference in the grade of hydrocephalus between the patients who had total tumor resection (as judged by postoperative neuroimaging) and those in whom total resection was not achieved (Mann–Whitney U-test; $z = -2.55$, $p = 0.01$), such that complete tumor resection was less likely the more severe the hydrocephalus. Similarly, the larger the tumor volume at presentation, the less likely was achievement of total excision, either as assessed by the surgeon at the time of
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operation ($z = -2.51$, $p < 0.02$) or by neuroimaging ($z = -2.01$, $p < 0.05$).

**Morbidity and Morbidity Score After Initial Surgery.** The morbidity scores for each clinical parameter after initial surgery and at study assessment are shown in Table 2. There were no deaths within the first 3 months of surgery. Of the 10 children who had evidence of severe neurological dysfunction in the initial postoperative period, seven had operative complications recorded at the time of surgery.

Only one patient had intact pituitary function after surgery. Seventy children had postoperative diabetes insipidus; this was permanent in 60 cases. An absent or impaired sense of thirst greatly complicated postoperative management in 10 children. All of these children had other evidence of hypothalamic dysfunction and all but one had undergone attempted complete excision of tumor from the hypothalamus.

**Tumor Recurrence.** Tumor recurrence, defined as evidence of tumor growth on neuroimaging with or without clinical symptoms, occurred in 31 patients ($41\%$) within 1 to 10 years (median 2 years) of initial surgery. Only three recurrences occurred after complete tumor excision (as determined by postoperative neuroimaging). The 5- and 10-year recurrence-free survival for the 29 cases with complete tumor excision was $89\%$ and $78\%$, respectively, compared with $32\%$ and $28\%$ for the incomplete excision group (log rank test, $p < 0.00001$) (Fig. 2). The patients with large-volume tumors or severe hydrocephalus at presentation were more likely to experience tumor recurrence (Mann–Whitney U-test; $z = -2.85$, $p < 0.005$ and $z = -3.15$, $p < 0.002$, respectively). The overall mean morbidity score at study assessment was significantly higher (Student’s unpaired t-test, $p = 0.001$) for children with tumor recurrence than for those without. Their mean score was already higher ($p < 0.05$) after initial surgery and before recurrence.

**Radiotherapy.** Fifteen patients received conventional cranial irradiation and one intracystic administration of yttrium-90 following initial subtotal tumor excision (12 cases), debulking or cyst aspiration (three cases), or total removal (one case) (Fig. 1). The mean morbidity score at study assessment for those children who received elective radiotherapy after subtotal tumor excision was not significantly different from those patients who had a complete tumor removal (on neuroimaging) and no radiation therapy. By the time of follow-up assessment, 38 children (age range 4.0–13.6 years at start of treatment) had received radiotherapy, 22 following tumor recurrence. Total dose regimens ranged from 40 to 60 Gy (median 50 Gy). Nine patients developed tumor recurrences despite undergoing radiation therapy; the recurrences appeared either during treatment or within 6 months of treatment in six cases, after which the tumor “stabilized” in five cases. There was no difference between the maximum tumor doses received in patients who developed recurrences and those who did not (median 50 Gy for both groups). Actuarial 10-year recurrence-free survival after radiotherapy (including treatment given for recurrent disease) was $72\%$ at a median follow-up assessment of 7.6 years.

**Additional Surgery.** Eighteen children, 14 of whom had radiotherapy after the additional surgery, underwent second craniotomies for tumor recurrence. Morbidity scores at study assessment for these 14 children were significantly higher than after their initial surgery (Student’s unpaired t-test, $p < 0.01$) and higher than in children without tumor recurrence ($p = 0.02$).

**Morbidity Score at Assessment.** By the time of the study assessment, nine children had died from their tumor or related sequelae, giving a 10-year actuarial survival of $88\%$ at a median follow-up review of 5.2 years. All but three of the children who died had total morbidity scores of 12 or greater after their initial operation, although the median time until death in these patients was 8.5 years (range 0.3–15.4 years). At study assessment, no survivors had the maximum morbidity score of 15, although 13 patients (20\%) had scores between 10 and 14.

**Risk Factors**

**Predictive Factors for Outcome Assessed by Morbidity Score.** Using forward stepwise multiple regression analysis to identify features at presentation and at operation that predicted a poor postprimary treatment outcome, the regression models with eight explanatory variables are shown in Table 4. The number of intracranial compartments involved by tumor was included as a measure of tumor size rather than tumor volume because the latter, although more specific, was only determined in 51 cases. Severe hydrocephalus and the occurrence of intraoperative complications were predictors of high morbidity both after initial surgery and at study assessment. Hypothalamic disturbance and young age at presentation were predictors of poor outcome after primary surgery (see also Hypothalamic Morbidity) and at long-term follow up, respectively.

**Predictive Factors for Tumor Recurrence.** To identify risk factors for tumor recurrence, Cox’s regression model was used with the same eight explanatory variables, together with the extent of surgical resection assessed by neuroimaging and whether radiotherapy was given elec-
Table 4: Forward stepwise regression models* used to predict short- and long-term morbidity after initial surgery and at study assessment as outcome variables

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Coefficient b (standard error (b))</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>morbidity score after initial surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade of hydrocephalus</td>
<td>0.94 (0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hypothalamic disturbance</td>
<td>2.44 (0.88)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>intraop complications</td>
<td>1.86 (0.76)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>morbidity score at study assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade of hydrocephalus</td>
<td>1.45 (0.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>intraop complications</td>
<td>1.97 (0.53)</td>
<td>0.02</td>
</tr>
<tr>
<td>age ≥5 yrs at presentation</td>
<td>1.87 (0.79)</td>
<td>0.02</td>
</tr>
<tr>
<td>tumor recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age ≥5 yrs at presentation</td>
<td>0.85 (0.39)</td>
<td>0.03</td>
</tr>
<tr>
<td>no. of intracranial compartments involved by tumor</td>
<td>0.66 (0.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>elective radiotherapy</td>
<td>−1.57 (0.54)</td>
<td>0.004</td>
</tr>
<tr>
<td>complete tumor excision</td>
<td>−3.19 (0.77)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Cox regression model (forward stepwise) used for predictive factors of tumor recurrence. Class variables included in analysis: age at presentation: $A_1$ (= 1 if ≤ 5 years, 0 otherwise); $A_2$ (= 1 if > 5 and ≤ 10 years, 0 otherwise); intraoperative complications (= 1 if yes, 0 if no); emergency presentation (= 1 if yes, 0 if no); grade of hydrocephalus (ordered from 1 to 4, 0 if none); hypothalamic disturbance (= 1 if yes, 0 if no); number of intracranial compartments involved by tumor (ordered from 1 to 7); tumor adherence (= 1 if yes, 0 if no); tumor components (= 1 if mainly solid, 0 otherwise); complete tumor excision on neuroimaging (= 1 if yes, 0 if no); elective radiotherapy after initial surgery (= 1 if yes, 0 if no). Complete tumor excision on neuroimaging and elective radiotherapy after initial surgery were used only in the Cox’s regression model to identify risk factors for tumor recurrence.

Discussion

Controversies of Management

Craniopharyngiomas are histologically benign tumors and thus potential cure and long-term survival with minimal morbidity should be realistic goals of management. Outcome following treatment, however, remains difficult to interpret because studies are nonrandomized and frequently specialty biased; discrepant results occur even when the same treatment modality is advocated as the optimal management; advances details concerning the quality of survival are often sparse, particularly with regard to hypothalamic function. By undertaking a critical analysis of outcome both in terms of tumor recurrence and short- and long-term morbidity, our study has defined certain prognostic factors that may assist in an individualized treatment approach.

Tumor Cure Versus Morbidity

Our analysis of outcome shows that although morbidity and tumor recurrence are interrelated, the two are not synonymous. Thus, a child “cured” of his or her disease may be crippled by consequent hypothalamic damage, as has been poignantly illustrated by Katz’s follow-up data of Matson’s and Crigler’s original series of patients. In our series, the 56% of patients with evidence of hypothalamic dysfunction at assessment (as distinct from hypothalamic pituitary hormone deficiencies) and, particularly, the 16% with severe hypothalamic syndromes contributed significantly to overall morbidity and mortality rates. Morbidly obese or chronically hyperosmolar children with an aberrant sense of thirst were seen almost exclusively after radical surgery; our figures compare with the disabling hypothalamic damage found in up to 57% of cases in various reported series.

Tumor Recurrence

Extent of Surgery. Craniopharyngiomas are highly resilient tumors that may recur from minute fragments left behind. Postoperative neuroimaging using a combination of CT and MR techniques is the only way to accurately assess the completeness of tumor resection when this was the aim of surgery. Hoffman and colleagues previously distinguished the small fleck of calcification that appears on MR images from enhancing tumor when defining residual disease but found with continued follow-up eval-

morbidity was found to be significantly higher in the former group ($z = −2.74, p < 0.01$). In 17 cases tumor was recorded as being adherent to the hypothalamus at surgery. In six of these cases the tumor component involving the hypothalamus was electively left alone when found to be adherent to this region. When these cases were excluded from the group with adherent tumor, a significantly higher morbidity rate was found in the patients in whom removal of adherent tumor had been attempted ($z = −2.20, p < 0.03$) compared to the group with nonadherent tumor. Whether the tumor in the hypothalamic region was cystic, solid, or mixed did not significantly influence morbidity.

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management of childhood craniopharyngioma

In our analysis, we found recurrences in only three of 29 patients following neuroradiologically confirmed total resection, which demonstrates the effectiveness of complete excision in terms of tumor cure.

Radiotherapy. In addition to complete tumor excision, radiotherapy given electively after initial surgery was an independent factor found to limit the likelihood of recurrence in our study. There is now a wealth of data to show that excellent long-term tumor control may be achieved using adjuvant irradiation; however, the plane of measurement has not been specified or only one or two tumor dimensions have been documented. Assessment of tumor volume in our patients confirmed a higher rate of recurrence in larger lesions and also showed that these were the tumors less likely to be totally excised, as determined by postoperative imaging.

Age at Presentation. Over one-third of the children in our series were under 5 years of age at presentation and represent an important group. Cranial irradiation usually cannot be considered as an adjuvant treatment in young children because of its age-dependent effect on cognitive function. In our study, young age was significant as a poor prognostic factor for long-term outcome as well as a risk factor for tumor recurrence. Choux, et al, reported a higher tumor recurrence rate in children under 5 years old and Rajan and colleagues demonstrated a linear trend of improved disease (and treatment)–related survival with increasing age.

Hydrocephalus. Severe hydrocephalus proved to be a significant prognosticator of poor outcome in our study with respect to tumor control and short- and long-term morbidity.

Patient Morbidity

Neurosurgical Experience. One disadvantage of our study is that several neurosurgeons performed the operations in our patient cohort. The operative experience of the neurosurgeon has been shown to be a major determinant of outcome in childhood craniopharyngioma. In a recent North American survey, surgeons operating on one child or fewer per year achieved a “good outcome” after radical surgery only 50% of the time, compared to surgeons averaging 2.25 to 2.75 operations per year who got “good results” in 87% of cases.

Radiotherapy. Our findings at study assessment of no significant difference in morbidity after complete tumor excision without radiotherapy or subtotal excision with adjuvant irradiation concur with other studies’ results that these treatment modalities are comparable. Permanent radiation injury occurs in a predictable manner in terms of dose, volume, and fractionation administered. Consequently, accurately planned and focused treatment, using modern high energy machines and doses of radiation 55 Gy or less at 1.8 Gy or less per fraction, should minimize toxicity. Newer techniques such as stereotactic radiotherapy allow further precision in dose delivery.

Age at Presentation. Young age (≤ 5 years) has been posited as a predictor of high longer-term morbidity, presumably reflecting the increased likelihood of tumor recurrence in this age group and the more aggressive nature of the tumors that present in young children. Although radical surgery aimed at total tumor excision has been recommended as the optimal treatment in those children under 5 years of age at diagnosis, there may also be a place for delaying radiotherapy after more conservative surgery, particularly in the face of other risk factors for increased morbidity. Even though irradiation may be effective in the control of tumor recurrence, its use must be balanced against the potential risk of additional morbidity from progressive disease and from salvage surgery.

Hydrocephalus. Although no distinction was made regarding severity, Wen, et al, found that the presence of hydrocephalus signified a poor prognosis both in terms of tumor control and actuarial 5-year survival. Yasargil and associates reported a 38% mortality rate in children with hydrocephalus who required shunt placement prior to craniotomy. The grade of the hydrocephalus was the most significant factor determining outcome in our patients. Neurological deficit or coma at the time of presentation, extensive third ventricular involvement by tumor, and the decreased likelihood of total resection and, therefore, long-term tumor control must all contribute to the morbidity associated with severe hydrocephalus, emphasizing the need for earlier diagnosis in these children.

Hypothalamic Morbidity. Children with symptoms of hypothalamic disturbance already present at diagnosis and extensive tumor compression of the hypothalamus (as assessed by midline height of tumor on neuroimaging) represent an important prognostic group for long-term hypothalamic dysfunction, and the neurosurgeon should be alert to the risks of inflicting further damage at operation. Arguments continue as to whether there is a distinct plane of cleavage between tumor and adjacent neural tissue allowing “safe” dissection from the region of the floor of the third ventricle or whether hypothalamic infiltration by foci of tumor cells precludes total excision ever being achieved without increased functional disturbance.

Intraoperative Morbidity. Intraoperative morbidity is increased with aggressive surgery and may become manifest in the immediate postoperative period as cerebral ischemic damage secondary to major vessel injury or in the long-term as frontal lobe dysfunction and late-onset epilepsy. Even with the benefits of microsurgical techniques, the occurrence of intraoperative complications,
namely vascular or frontal lobe trauma in our patients, proved to be a significant predictor of high morbidity, as determined immediately after surgery and at long-term follow-up assessment. The additional surgical morbidity and mortality associated with second or subsequent attempts at radical surgery for tumor recurrence are also well known.6,21,39,40

Conclusions

Clinical and radiological risk factors at presentation may guide further neurosurgical management. If there are no adverse risk factors at presentation, an attempt should be made at total excision. However, if tumor is found to be adherent to hypothalamic tissue at operation, preservation of the hypothalamus should be the primary aim of surgery. If a child presents with symptoms and signs of hypothalamic disturbance and severe hydrocephalus secondary to an extensive craniopharyngioma, serious consideration should be given to the use of a limited surgical procedure designed to decompress the foramina of Monro and/or preserve vision, rather than risk additional vessel or hypothalamic injury by attempting a more radical tumor removal. Total tumor excision cannot be justified in every case, particularly as radiotherapy offers an effective alternative for prevention of additional morbidity from tumor recurrence. In young patients, irradiation may be deferred by performing staged conservative surgical procedures as necessary. Acceptance that certain tumors are surgically incurable from the outset may help preserve quality of life, particularly as survival in those patients in whom a high morbidity is predicted may be prolonged for many years. Treatment must be individualized and a multidisciplinary approach should be used both pre- and postoperatively in an attempt to provide long-term tumor control with the lowest morbidity.

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